REVIEW ARTICLE

Clinical and Imaging Evaluation of Nipple Discharge

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Nipple discharge, the spontaneous release of fluid from the nipple, is a common presenting finding that may be caused by an underlying intraductal or juxtaductal pathology, hormonal imbalance, or a physiologic event. Spontaneous nipple discharge must be regarded as abnormal, although the cause is usually benign in most cases. Clinical evaluation based on careful history taking and physical examination, and observation of the macroscopic appearance of the discharge can help to determine if the discharge is physiologic or pathologic. Pathologic discharge can frequently be uni-orificial, localized to a single duct and to a unilateral breast. Careful assessment of the discharge is mandatory, including testing for occult blood and cytologic study for malignant cells. If the discharge is physiologic, reassurance of its benign nature should be given. When a pathologic discharge is suspected, the main goal is to exclude the possibility of carcinoma, which accounts for only a small proportion of cases with nipple discharge. If the woman has unilateral nipple discharge, ultrasound and mammography are frequently the first investigative steps. Cytology of the discharge is routine. Ultrasound is particularly useful for localizing the dilated duct, the possible intraductal or juxtaductal pathology, and for guidance of aspiration, biopsy, or preoperative wire localization. Galactography and magnetic resonance imaging can be selectively used in patients with problematic ultrasound and mammography results. Whenever there is an imaging-detected nodule or focal pathology in the duct or breast stroma, needle aspiration cytology, core needle biopsy, or excisional biopsy should be performed for diagnosis. An excisional biopsy should be carried out with a thorough plan after a complete imaging evaluation. The evaluation of physiologic discharge or galactorrhea is primarily an assessment of endocrine factors.

KEY WORDS — biopsy, breast, magnetic resonance imaging, mammography, nipple discharge, ultrasound

■ *J Med Ultrasound* 2005;13(2):47–59 ■

Introduction

Nipple discharge is usually defined as fluid that escapes spontaneously from the nipple, while fluid in the ducts that must be collected by aspiration, suction or massage, i.e. does not escape spontaneously, is referred to as "secretion". Nipple discharge has been reported in 10–15% of women with benign

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breast diseases, and in about 1–3% of those with breast cancer [1,2]. The discharge, according to its appearance, can be described as milky, serous, greenish, brown, colored, cloudy, purulent, serosanguineous, or bloody. Among these, bloody discharge is the most worrisome because of its association with papillary lesions or carcinoma (Fig. 1). Only 4% of women with nipple discharge have breast cancer [3], although the reported incidences vary greatly [4–8]. However, in patients with bloody or serous nipple discharge, there is a higher prevalence of carcinoma, papilloma or other papillary lesions (74%). The majority (94%) of patients having fluid with secretory components were associated with fibrocystic changes and other nonproliferative breast lesions; only 6% were associated with papillomas [9]. It is, therefore, very important to evaluate the clinical significance of nipple discharge, especially when there is no palpable mass [9].

Clinical Evaluation of Nipple Discharge

Spontaneous nipple discharge is often ignored. Women search for medical help usually because of colored or bloody discharge. Generally, only a small percentage of women with nipple discharge are found to have malignancy. The majority of discharges are caused by benign conditions such as fibrocystic changes, duct ectasia, benign papilloma or other papillary lesions, or other nonproliferative lesions [9,10]. Evaluation of the discharge is mainly based on a careful history, physical examination, specific imaging studies, cytologic studies, and/or histopathologic studies.

History

A history of nipple discharge in association with a self-discovered mass is suggestive of neogrowth or cancer. The clinically significant discharge is usually spontaneous, not a result of forcible manual compression or passive induction. The discharge is also significant if it is unilateral, or localized to a single quadrant or a single duct, and occurs in an older woman. Discharges associated with cancer can be bloody, watery, serous or serosanguineous. Discharges due to benign causes are frequently bilateral and multiductal, and are usually milky, green or greenish blue [11]. Discharge as a sole finding without any palpable mass is rarely related to breast cancer [2]. Nipple discharge in a patient carrying risk factors such as a family history of breast cancer on the maternal side, or a past history of breast cancer, requires more vigilant investigation or close surveillance.

Physical Examination

In addition to routine inspection and palpation of the entire breast and lymph node-bearing area, the nipple-areola complex should be carefully inspected for subtle changes in the surface, retroareolar masses, and nipple discharge [3]. The physical examination is performed by first squeezing the nipple between the finger and thumb to check the character of the discharge. Then, the nipple is cleaned, and further forcible manual compression is applied to the breast from the peripheral to the central part according to the different clock directions, preferably radially in a clockwise fashion starting from the 12 o'clock position. A diagram is used to record the location of the duct or quadrant related to the discharge. We prefer to localize any mass or abnormalities along a specific radial of a clock on the breast in centimeters from the margin of the nipple attachment. The suspected area of abnormality can be marked on the skin with a skin marker, so that imaging studies can be correlated with the physical findings.

Specific Imaging Studies

Mammography

The majority of physicians agree that mammography is an effective screening tool. The benefit of detecting a small cancer using screening mam-

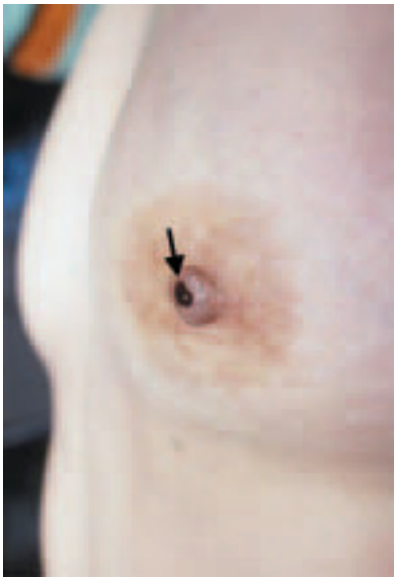

Fig. 1. *Typical clinical presentation of bloody discharge from the nipple (arrow).*

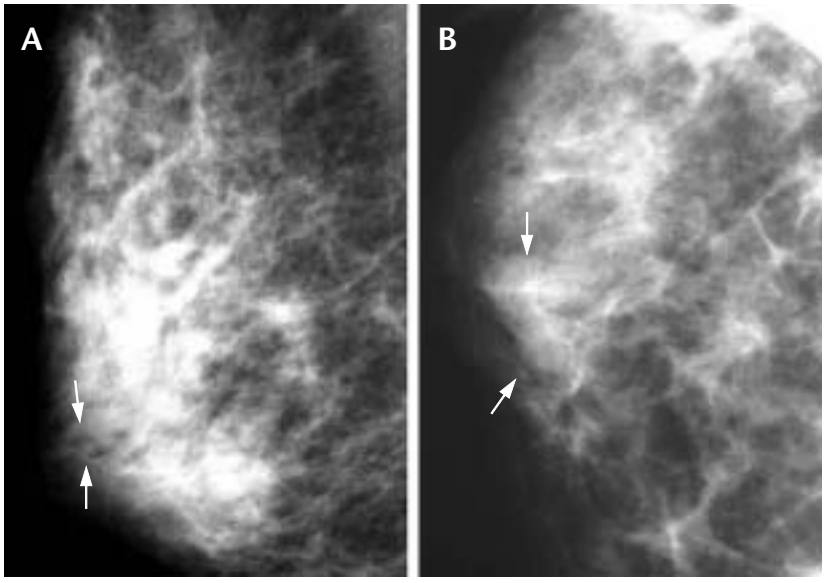

Fig. 2. *Mammograms of a 57-year-old woman with nipple discharge: (A) mediolateral oblique view shows prominent ducts (arrows) in the subareolar region; (B) magnified view better demonstrates the prominent ducts (arrows).*

mography far outweighs any theoretical risk [12, 13]. Therefore, in patients with nipple discharge, mammography is indicated if the woman is older than 40 years, especially when the patient has never had a mammography before the episode of discharge. Mammography may not demonstrate small intraductal nodules such as small papillomas or carcinomas which are not calcified. Dilated ducts caused by relatively small intraductal pathology in the subareolar region can be depicted (Fig. 2). Generally, the state-of-the-art ultrasound machine can provide high-resolution imaging to detect a dilated duct and, frequently, intraductal pathologies. We prefer to perform ultrasound first. Information from physical examination should be obtained before imaging, preferably with skin markings of any abnormalities suspected.

Ultrasound

Ultrasound has frequently been used as an adjunct to mammography in the diagnosis of breast diseases. It is most useful and accurate in the evaluation of dense breasts, when mammography has low sensitivity in tumor detection, and in differentiating between cystic and solid masses. By using state-of-the-art ultrasound scanners, small solid nodules that are even smaller than 5 mm can be visualized, and dilated ducts can be easily depicted (Fig. 3). The presence of intraductal echoes might suggest inspissated milk or a solid tumor, depending on the echogenicity and morphology of the intraductal echoes (Figs. 4–6). Generally, a breast with physiologic nipple discharge contains multiple dilated ducts, rather than a single duct as in pathologic discharge. The fluid inside the ducts is usually anechoic or very hypoechoic. In patients with pathologic discharge related to malignant tumors, the lesion, if identifiable on ultrasound, can be inside the dilated duct, adjacent to it, or invading into the duct and distending the lumen (Fig. 7). Color Doppler ultrasound can further provide information of the blood flow signals inside or peripheral to the dilated duct. When there are color flow signals in the intraductal echogenic nodule, neogrowth should be considered (Fig. 8). Contrast-enhanced ultrasound may increase the sensitivity in tumor detection and diagnostic confidence in color or power Doppler mode (Figs. 9 and 10).

Galactography

Injection of water-soluble iodinated contrast into the ducts via the duct opening may demonstrate

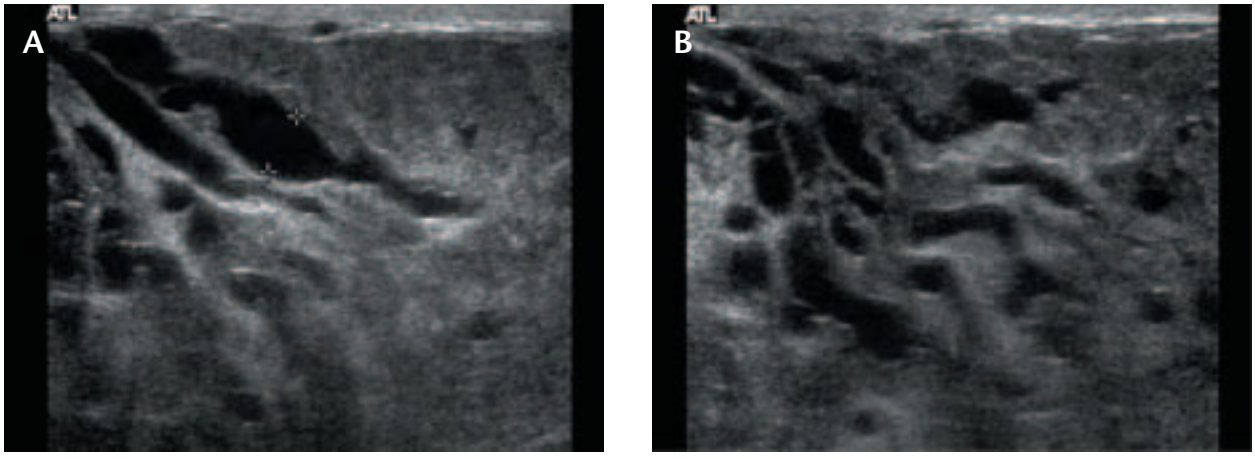

Fig. 3. *Dilated ducts in a lactating woman: (A) the ducts are smoothly dilated or mildly irregular in caliber; (B) the contents are usually echo-free or show only low-level echoes.*

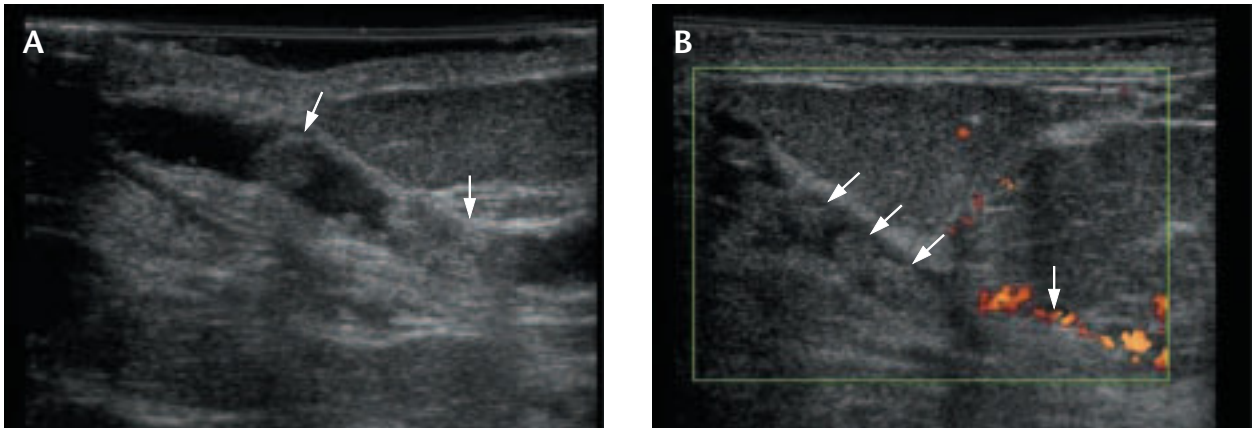

Fig. 4. *Dilated ducts in a 62-year-old woman contain concretions of inspissated milk (arrows): (A) left breast; (B) right breast – color Doppler ultrasound cannot demonstrate any color flow signal in the echogenic nodules in the ducts.*

Fig. 5. *A single dilated duct (arrow) located in the subareolar region contains an ovoid solid tumor (arrowhead) corresponding to an intraductal papilloma.*

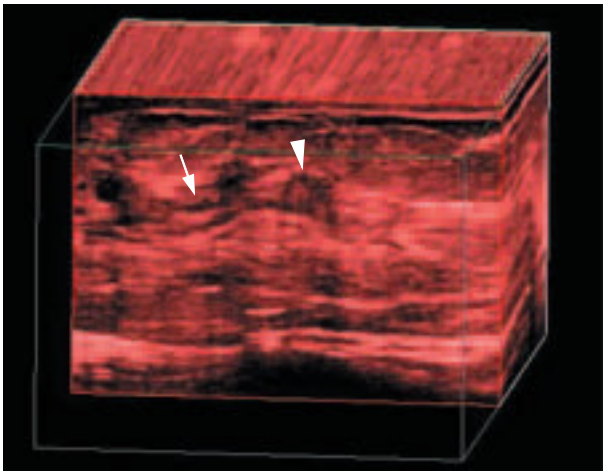

Fig. 6. *Three-dimensional ultrasound demonstrates a minimally prominent duct (arrow) with a solid tumor (arrowhead) located in the more peripheral portion. Surgical resection of the tumor confirmed the diagnosis of intraductal papilloma.*

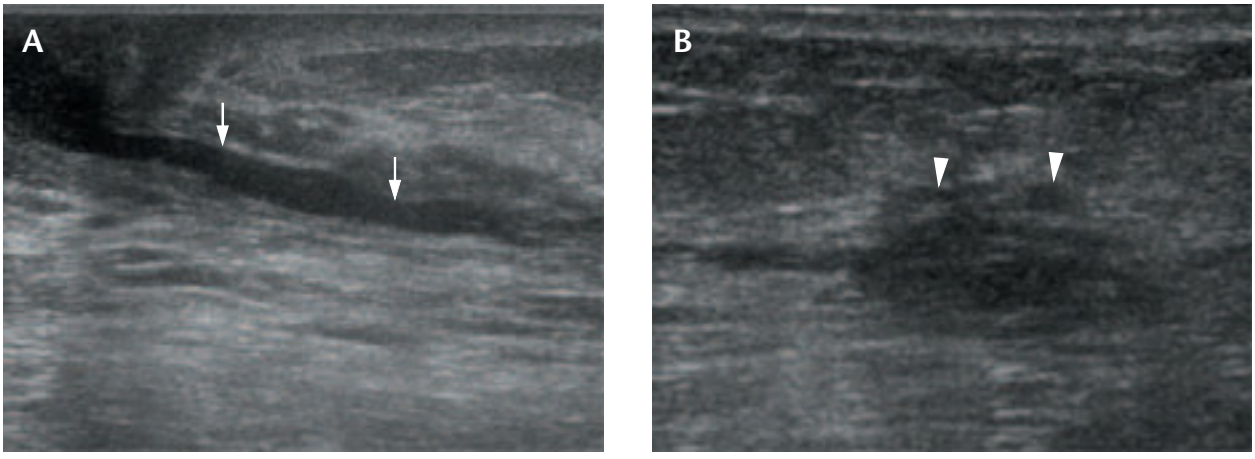

Fig. 7. *A 75-year-old woman with serous nipple discharge: (A) ultrasound shows a dilated duct (arrows) in the subareolar region; (B) while tracing towards a more peripheral portion of the breast, a small hypoechoic lesion with a poorly defined boundary is found (arrowheads), confirmed pathologically as a ductal carcinoma* in situ *with microinvasion.*

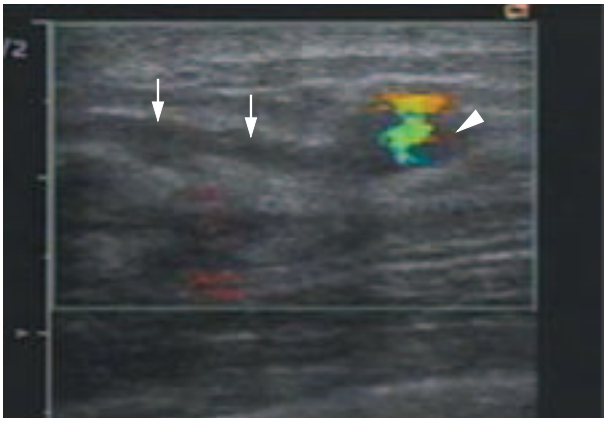

Fig. 8. *A small intraductal papilloma (0.8 × 0.6 cm) (arrowhead) and a dilated duct (arrows) are shown on color Doppler ultrasound; the color flow signals in the lesion are indicative of a solid tumor or a papilloma.*

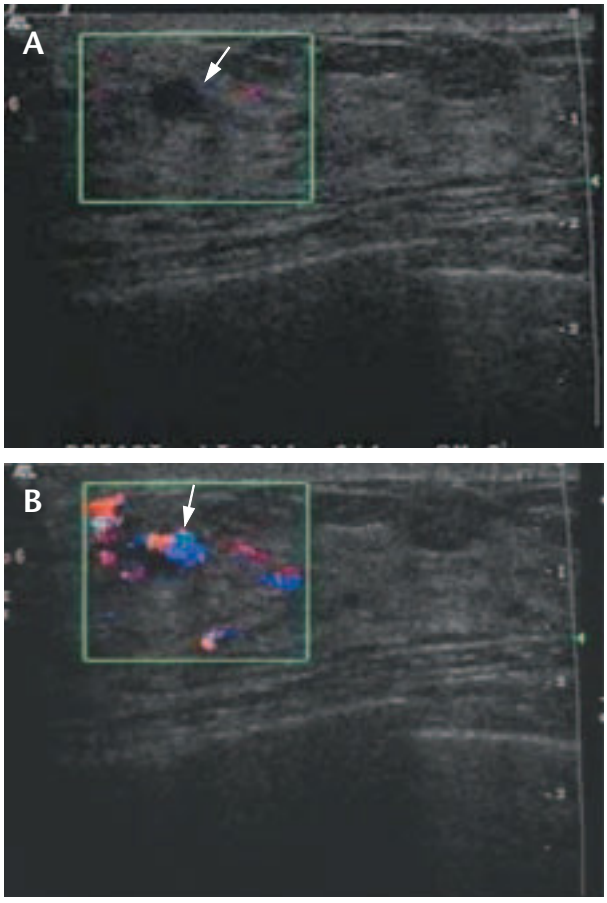

Fig. 9. *(A) A nonpalpable small subareolar nodule (0.6 cm) (arrow) contains minimal color flow signals on color Doppler ultrasound. (B) After intravenous injection of microbubble ultrasonic contrast agent (Levovist®), the nodule is well enhanced, and profuse color flow signals are demonstrated 20 seconds after contrast injection. The nodule is pathologically proven to be a papilloma.*

duct ectasia, obstruction, galactocele or filling defects (Figs. 11–13). This test is useful in experienced hands. A method of combined galactography with wire localization has been introduced to find papillomas [14], but the procedure is somewhat complicated and there is no reliable means of intraoperative verification that the correct tissue has been removed; it is, therefore, not strongly recommended nowadays. Even galactography is now seldom used because it is time-consuming and often painful [15].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is being studied to determine its usefulness in diagnosing breast

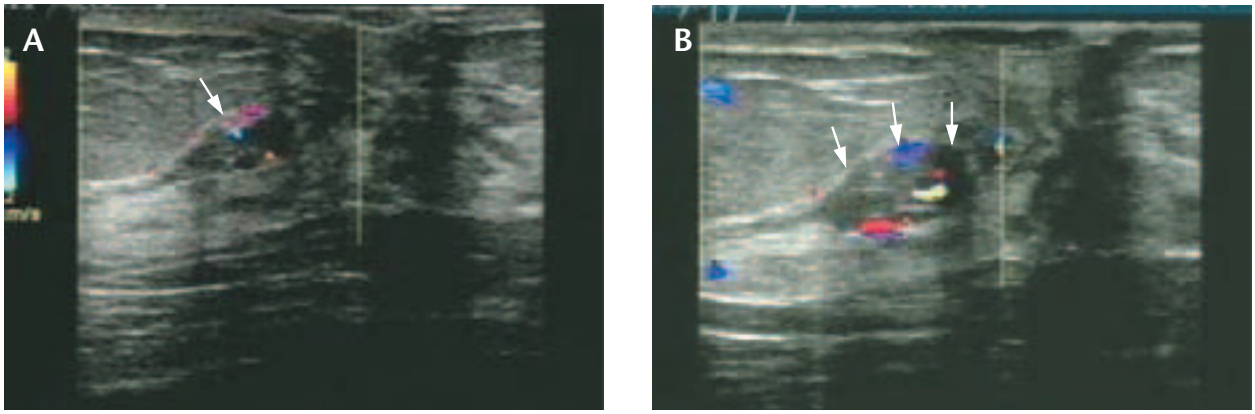

Fig. 10. *A small subareolar intraductal carcinoma (0.8 × 0.6 cm) in a 52-year-old woman with bloody nipple discharge. (A) Before contrast injection, the lesion (arrow) shows only minimal color flow signals; (B) after contrast injection, profuse color flow signals are noted in the lesion (arrows).*

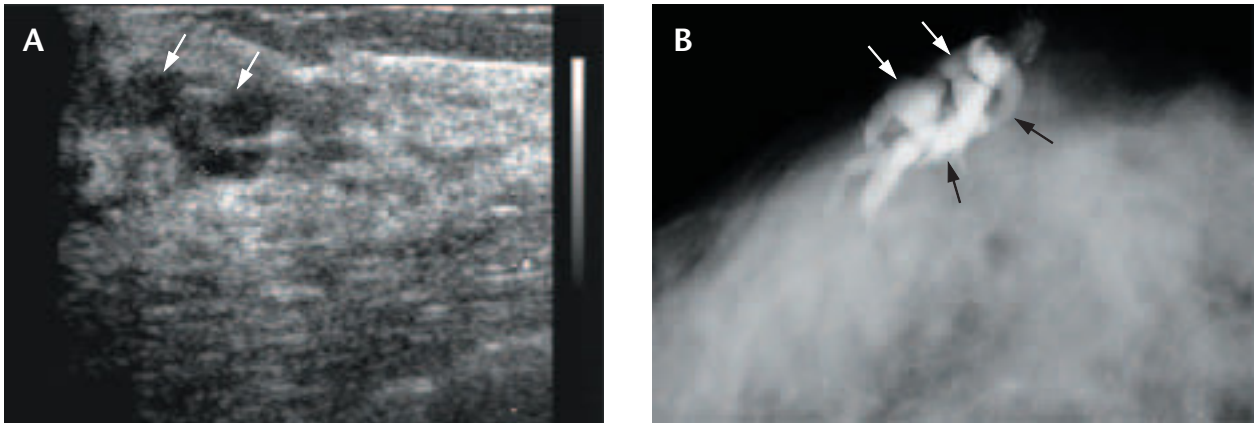

Fig. 11. *Focal dilatation of ducts in the left breast of a 32-year-old woman with yellowish nipple discharge. (A) Ultrasound shows multiple dilated ducts (arrows) in the left upper outer quadrant (mainly at 2 and 3 o'clock directions). (B) Galactography with injection of water-soluble iodinated contrast agent demonstrates the dilated ducts without visible intraductal filling defects (arrows).*

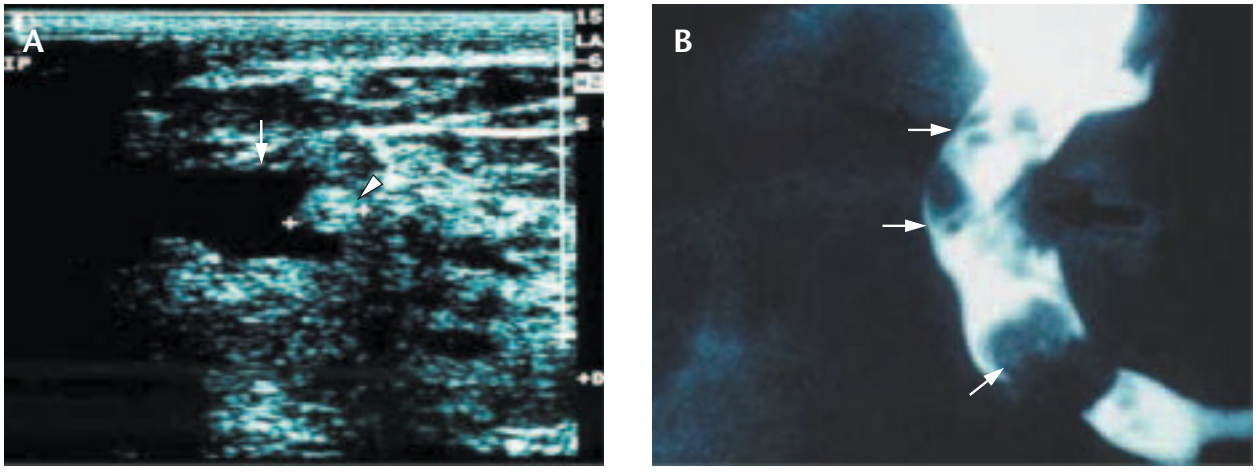

Fig. 12. *Intraductal papillomas within a single dilated duct. (A) Ultrasound depicts a dilated duct (arrow) and an intraluminal nodule (arrowhead), indicating a tumor – most likely papilloma. (B) Galactography shows multiple filling defects in the dilated duct; more nodules (arrows) can be demonstrated by galactography.*

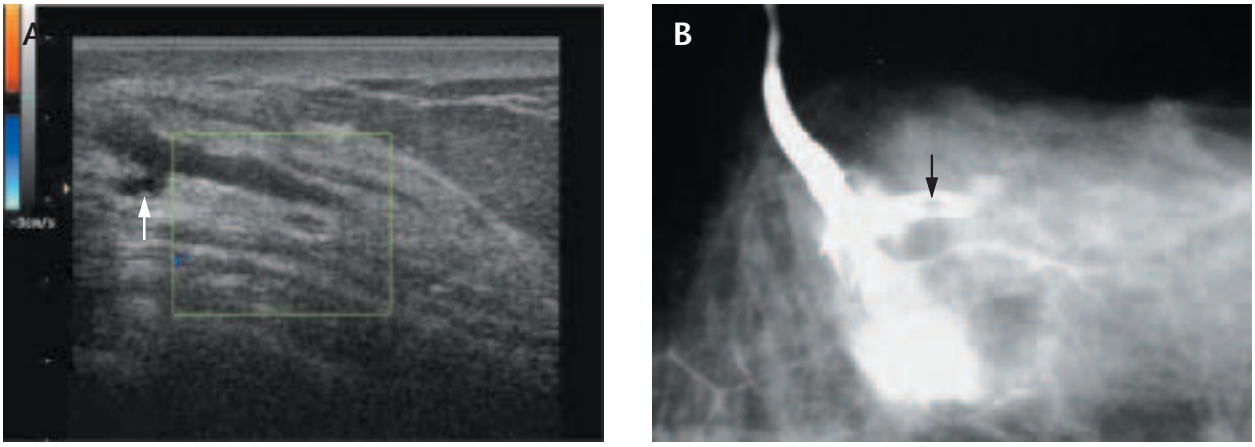

Fig. 13. *A tiny intraductal papilloma is demonstrated on: (A) ultrasound (arrow); and (B) galactography (arrow).*

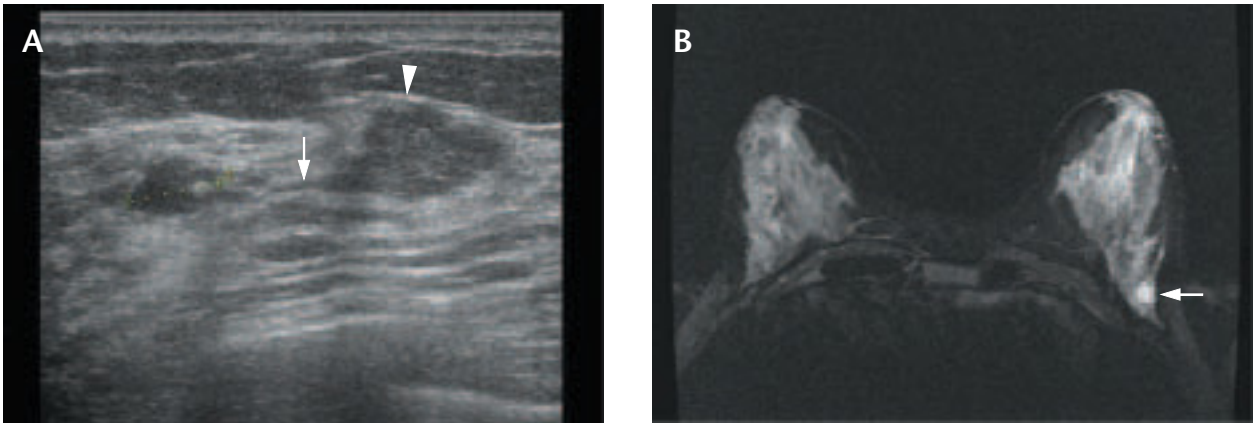

Fig. 14. *A 58-year-old woman with nipple discharge from the left breast and a palpable nodule in the left 2 o'clock direction. (A) Ultrasound demonstrates the solid tumor (arrowhead) and a minimally dilated duct (arrow) adjacent to it. (B) Dynamic contrast-enhanced magnetic resonance imaging also shows the rapidly enhanced tumor (arrow), but the adjacent duct is not shown on T2 imaging.*

masses. Gadolinium contrast is used to enhance the vascularity of malignant lesions. Although MRI is highly sensitive (85–100%), it lacks specificity (47–67%) [16,17]. MRI is inferior to mammography in detecting *in situ* cancers and cancers smaller than 3 mm, and it provides no cost benefit over excisional biopsy for verifying malignancy [16,17]. Research suggests two potential roles for MRI in breast mass diagnosis: evaluating patients with silicone breast implants [18], and assessing patients in whom evaluation by ultrasonography and mammography is problematic. There is no concrete evidence thus far that MRI can be effectively used in detecting intraductal pathologies, although the potential definitely exists (Figs. 14–16). There are limited reports on the MRI characteristics of breasts with abnormal discharge. Findings including rapid contrast enhancement of intraductal papillomas or small luminal mass with nonspecific MRI patterns have been described [19,20]. In a retrospective review of 15 pathologically proven papillomas, three patterns were found. Four papillomas were small, smooth, enhancing masses at the posterior end of an enlarged duct, corresponding to the "small luminal mass" appearance of papilloma known from galactography; two of these "small luminal mass" papillomas in patients with abnormal discharge were detected on MRI even when galactography was unsuccessful. Seven papillomas showed irregular enhancing masses without specifically benign

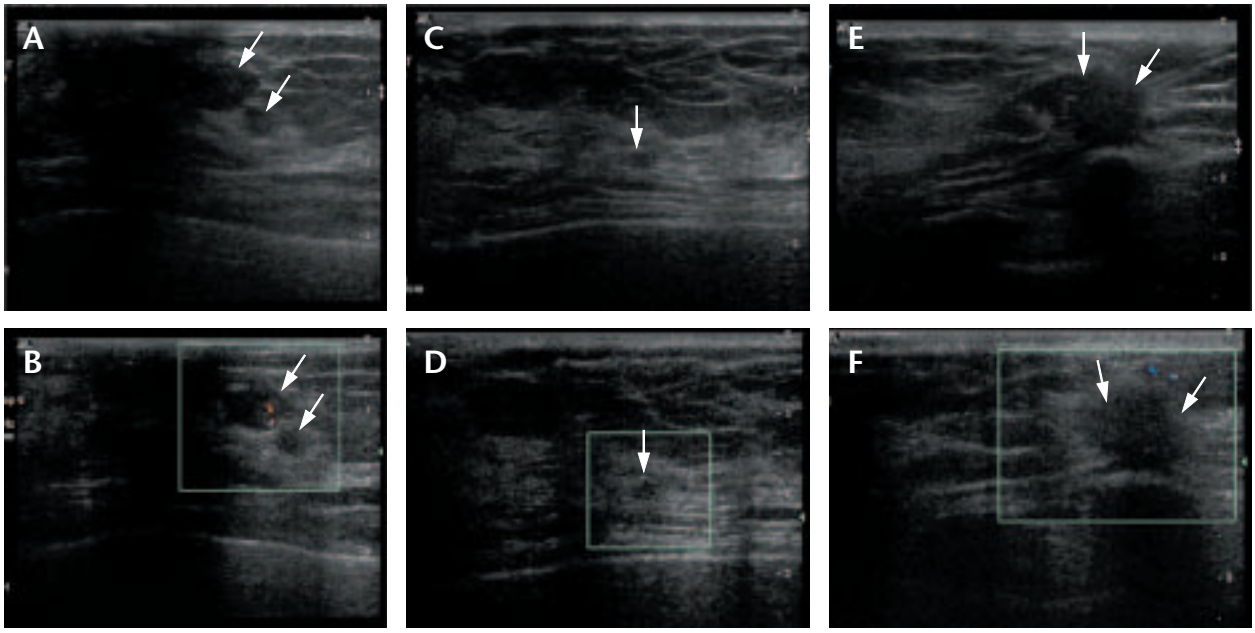

Fig. 15. *Sonography of the right breast in a 58-year-old woman with confirmed papillomas and cancer. (A) Two hypoechoic nodules (arrows) in the right subareolar region, measuring 1.0 cm and 0.5 cm. (B) Color Doppler ultrasound of the subareolar lesions (arrows) demonstrates minimal color flow signals in the larger lesion, while the smaller lesion shows no significant signals. (C) One of the other small nodules in the breast is also shown (arrow); (D) but no significant color flow signals can be demonstrated on color Doppler ultrasound. (E) Grayscale and (F) color Doppler ultrasound depict a solid tumor (arrows) in the right breast over the medial aspect. The lesion has an indistinct boundary and spiculated margin, indicative of a malignant tumor. Color Doppler ultrasound shows no significant color flow signals in the lesion, but minimally increased blood flows in the surrounding tissue are evident.*

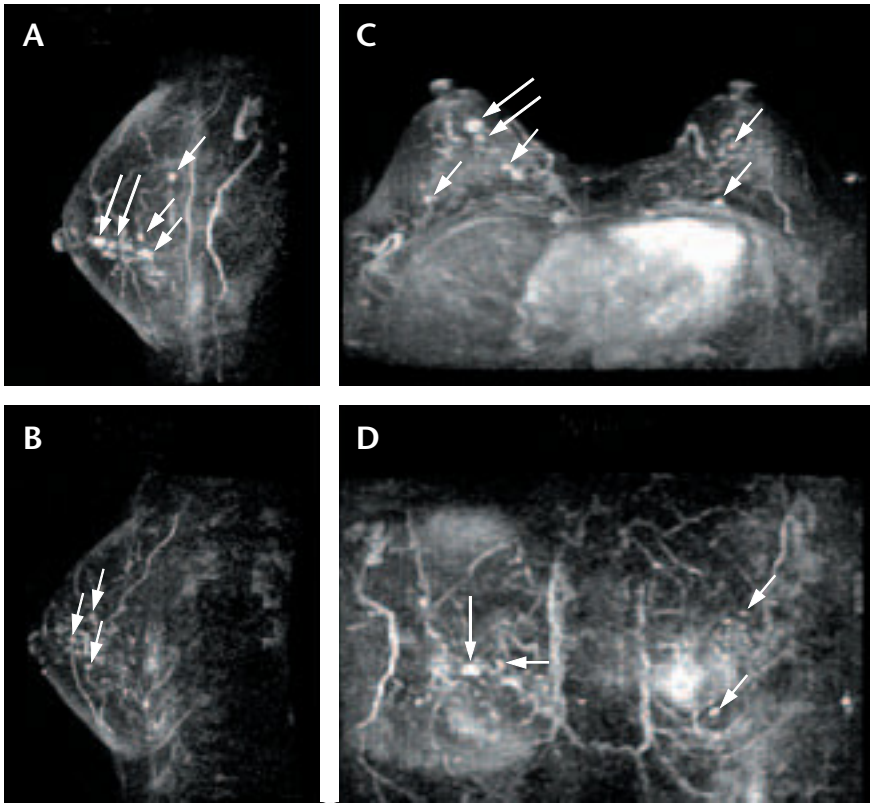

Fig. 16. *Dynamic contrast-enhanced magnetic resonance imaging (MRI) of the same patient as in Fig. 15. Early arterial phase, maximum intensity projection: sagittal images of the (A) right breast and (B) left breast; (C) axial image of bilateral breasts; and (D) frontal image. All demonstrate the rapidly well-enhanced subareolar papillomas (large arrows) and other small papillomas (small arrows). The cancer in the medial aspect of the right breast is, however, poorly demonstrated on MRI.*

findings. All seven demonstrated rapid enhancement and three showed rim enhancement or speculation. These "tumor-like" papillomas, however, could not be distinguished from invasive breast cancer on MRI. Four papillomas were occult on MRI, not revealed by either contrast-enhanced MRI or fat-suppressed T2-weighted MRI [17]. On the basis of these observations, MRI can be of certain aid in the evaluation of patients with abnormal nipple discharge that is caused by intraductal papillomas.

Cytologic and Histologic Studies

Nipple discharge / aspirate fluid cytology

Nipple discharge may be episodic, and when the patient presents herself to the physician, there may not be spontaneous discharge. In a large proportion of women, fluid in the dilated duct lumens can be obtained by removing the keratotic plug and using the "finger-and-thumb" test or a simple nipple aspirator device [21–23]. After eliciting the discharge, the aspirate fluid can be smeared onto a glass slide, fixed, and submitted for cytologic evaluation with Papanicolaou stain [24]. An air-dried smear with Wright's or Liu's stain may also provide some information [25]. The cytopathologist or pathologist who makes the final diagnosis should review all the available slides. They should make their interpretation based on the cytologic findings, together with knowledge of the clinical information. The basic experience can be accumulated partly from a knowledge of cytologic findings in the discharge or aspirate fluid of women without breast disease (i.e. normal or benign findings) [26,27]. Cytology has been reported to have a false negative rate of 18% and a false positive rate of 2.5% [11].

Ultrasound-guided aspiration cytology

Needle aspiration cytology involves the use of a fine needle (usually 22 gauge or smaller) with a syringe to aspirate the contents inside a dilated duct or to directly target an intraductal nodule to obtain cells for analysis. The aspirated material can be smeared onto glass slides and fixed immediately in 95% ethanol, then stained for cytologic evaluation (Figs. 17 and 18). Some experts also request air-dried smears. If the procedures of aspiration and specimen preparation are performed accurately and the cytopathologist is experienced, a high yield rate from cytologic study for the diagnosis can be achieved. A limitation to this technique is the inability to obtain a specific histologic diagnosis [28, 29].

Core needle biopsy

Core needle biopsy (CNB) produces a larger tissue sample than fine needle aspiration (FNA), and may be used in conjunction with ultrasonography or stereotactic imaging for small or difficult-to-palpate lesions. Local anesthesia is required. A 14- to 18-gauge cutting needle is used to obtain two to six

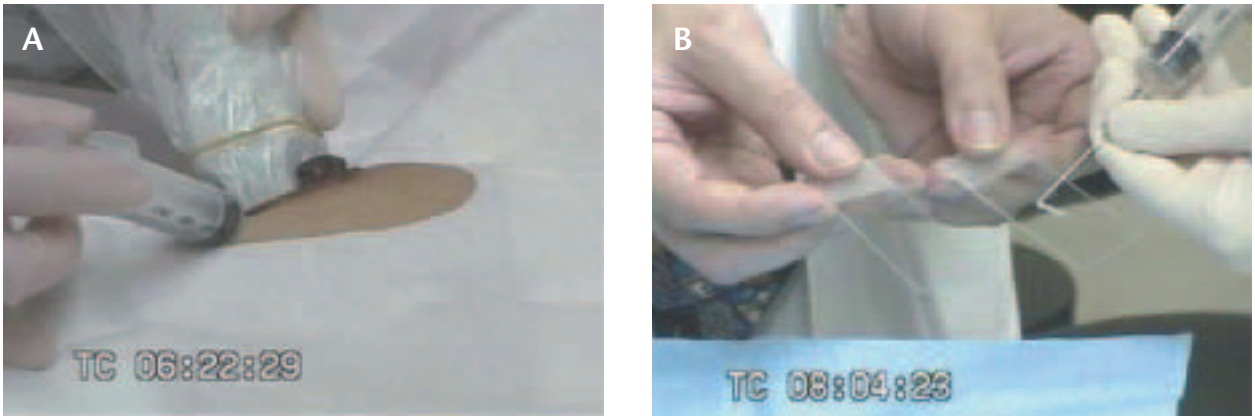

Fig. 17. *Ultrasound-guided aspiration cytology. (A) Needle insertion and aspiration are monitored by high-resolution ultrasound. (B) The aspirated fluid or material is sprayed onto a glass slide and then smeared for cytologic study.*

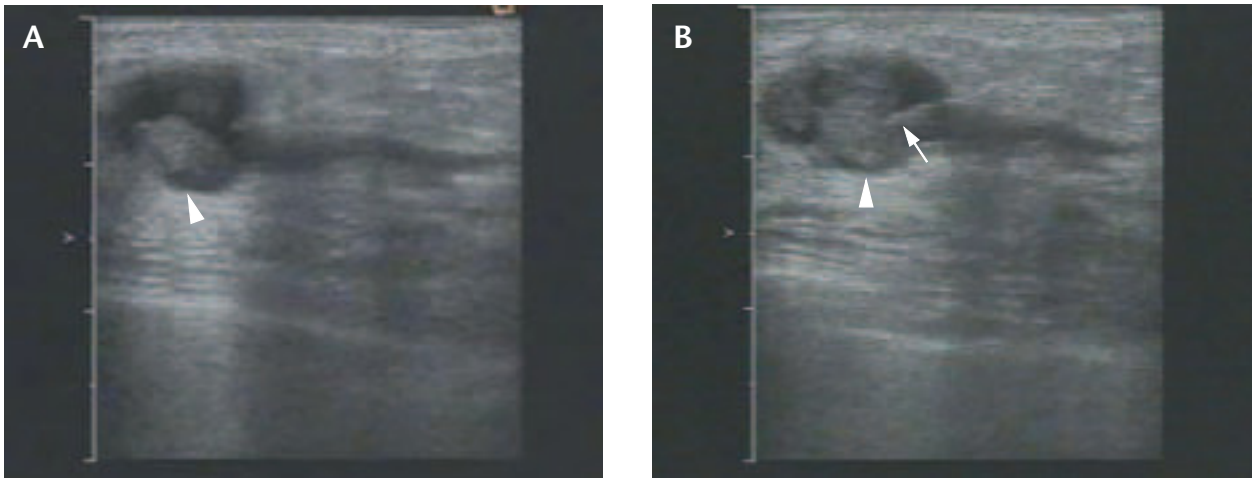

Fig. 18. *Needle aspiration targeted at an intraductal tumor (papilloma). (A) The duct is focally dilated in the subareolar region, with an intraductal solid tumor (arrowhead). (B) The needle tip (arrow) is guided to directly target the tumor (arrowhead).*

slender cores of tissue for histology [30,31]. The sensitivity of ultrasound-guided CNB may be as high as 99% in diagnosing malignancy in palpable lesions and 93% in nonpalpable lesions [32]. However, application of CNB for intraductal contents is not routinely used in our hospital. We prefer to perform FNA first; if there is any doubt, CNB or wire localization for surgical removal of the duct and its contents can be undertaken. Part of the reason for this is because intraductal pathologies are usually quite small, and they can be pushed away by the relatively blunt larger-bore needle. If a lesion with a size of 4–5 mm or larger is demonstrated on ultrasound, inside or adjacent to the duct, or in the breast stroma, then CNB can be confidently performed (Figs. 19 and 20).

Excisional biopsy

Excisional biopsy can be diagnostic and therapeutic: a completely removed mass with good margins of normal tissue may mean that further surgery is not required. Excisional biopsy is indicated in patients with clinically suspicious lesions and lesions in which imaging or tissue studies are equivocal [33,34]. With the increased use of CNB, the need for diagnostic excisional biopsy has declined, particularly in malignant tumors [35].

Excisional biopsy should be carried out as part of a thorough plan, usually starting with a complete whole breast ultrasound and mammography study.

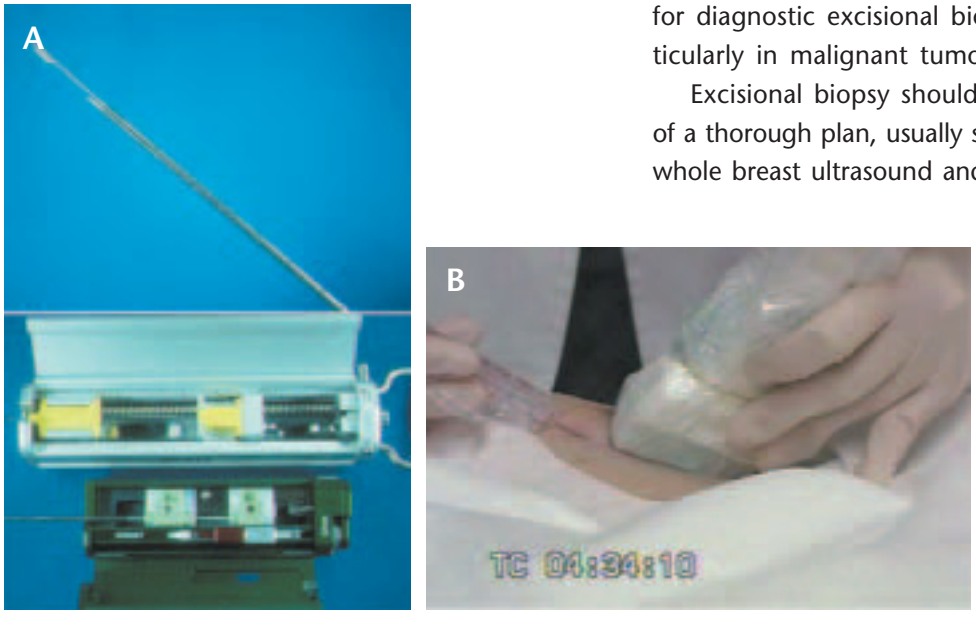

Fig. 19. *Needle biopsy: devices and procedure. (A) The needle used in core needle biopsy (upper panel) and the biopsy guns (lower panel). (B) Ultrasound-guided needle biopsy procedure using a disposable needle.*

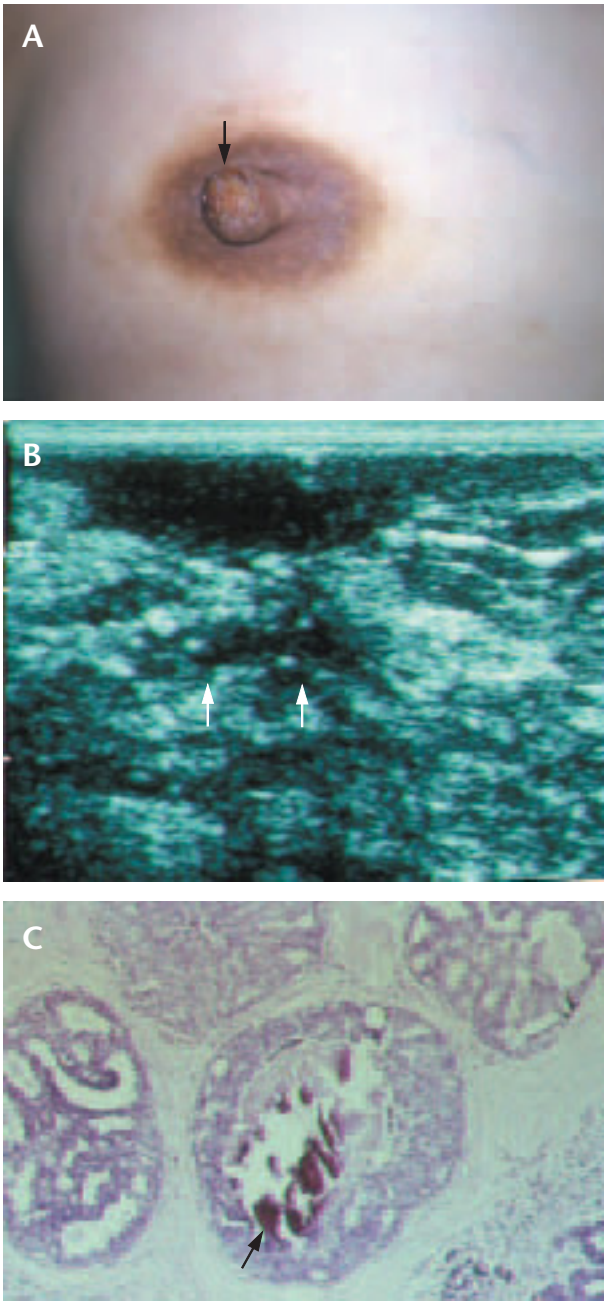

Fig. 20. *A woman with Paget's disease with oozing from the nipple. (A) The nipple has an eczematous appearance. (B) Ultrasound shows microcalcifications in the subareolar region, probably inside the minimally dilated ducts (arrows). (C) Histologic study of the biopsy specimens reveals a pattern of ductal carcinoma* in situ *with microcalcification (arrow).*

If ultrasound shows a dilated duct with a definite solid nodule inside or adjacent to the dilated duct, and whole breast ultrasound and mammography show no other suspicious malignant pathology, ultrasound-guided wire localization can be performed (Fig. 21). Planning all incisions and then removal of all the gross evidence of disease (including dilated duct and nodule), usually with a small rim of normal breast tissue, should be performed carefully, since there can be a need for subsequent surgery if the lesion is found to be malignant on frozen section.

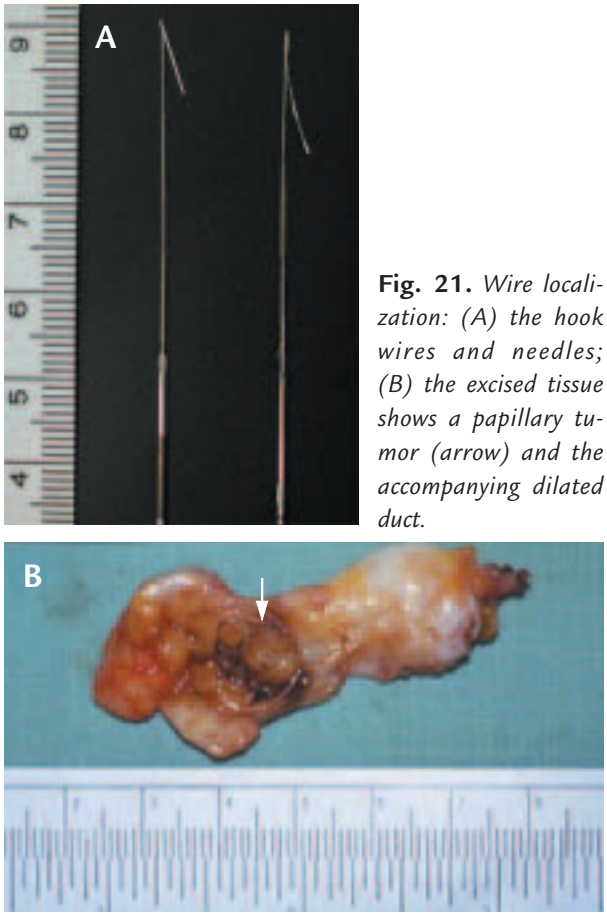

Fig. 21. *Wire localization: (A) the hook wires and needles; (B) the excised tissue shows a papillary tumor (arrow) and the accompanying dilated duct.*

General Comments on Treatment Plan

As bilateral and multiductal discharge are unlikely to be associated with cancer, investigations should basically focus on function tests, serum prolactin level, and checking for medication history, e.g. hormone replacement therapy, psychotropics and antihypertensive drugs. Treatment is mainly for the patient's underlying conditions. Any discharge should be routinely checked for occult blood. An occult blood-positive discharge does not neces-

sarily indicate malignancy, but suggests intraductal disease. Further studies should be done to detect intraductal and/or intraparenchymal tumor, especially if the discharge is from a single duct. If cytologic study of the discharge or aspirated fluid shows no evidence of malignant or suspect cells, and imaging studies do not demonstrate any focal solid lesion that can be related to the dilated ducts or occult blood-positive discharge, the patient can be treated conservatively. However, for patients with purulent or green and sticky discharge in the absence of subareolar induration or mass, the administration of antibiotics should be considered. Women can be very fearful if they have both nipple discharge and mastalgia. If all the investigations demonstrate no evidence of breast tumor, most patients require no active treatment. In women suspected of having periductal mastitis, nonsteroidal anti-inflammatory drugs can be tried [27].

Conclusion

Whenever there is imaging evidence of a focal solid breast nodule, the treatment plan should follow the general algorithm for the diagnosis and treatment of breast cancer. Physicians who are involved in the diagnosis and treatment of patients with nipple discharge should remember that delayed diagnosis of breast cancer has been one of the most expensive conditions for insurance companies in the United States since 1995. This may also begin to happen in Asia. Physicians should take any symptoms of the patient seriously. Although only a small percentage of breast malignancy is associated with nipple discharge, proper investigations should still be undertaken.

Acknowledgments

The authors would like to thank Ms. Siew-Peng Chen, the senior research assistant, for her excellent assistance in some of the studies conducted during the past 4 years.

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